# AKT phosphorylates FOXO transcription factors

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# Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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## Literature references

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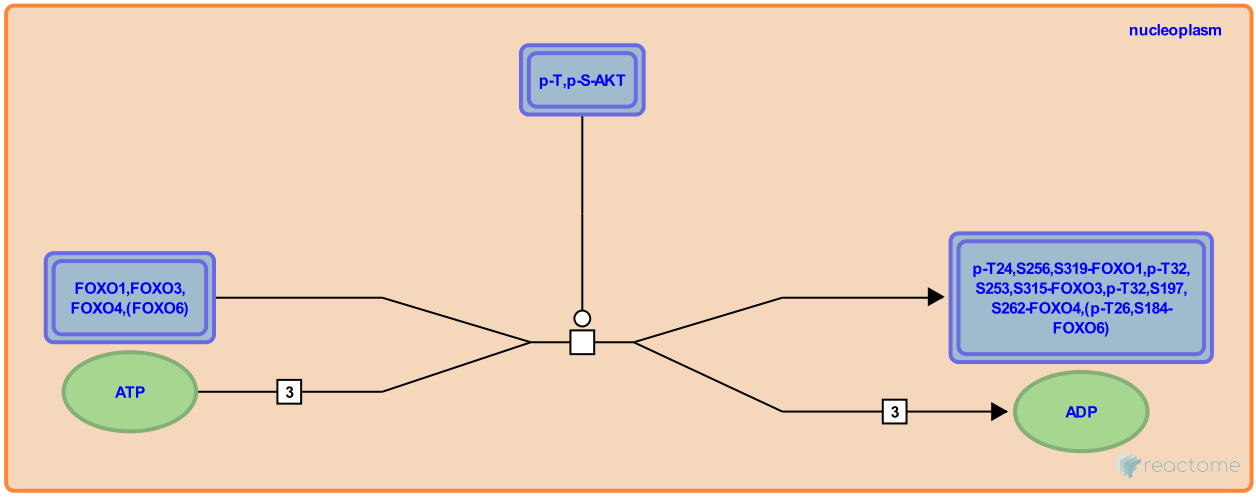
## AKT phosphorylates FOXO transcription factors ↗

**Stable identifier:** R-HSA-199299

**Type:** transition

**Compartments:** nucleoplasm




AKT-mediated phosphorylation of Forkhead box (FOX) transcription factors of the FOXO family, FOXO1 (FKHR), FOXO3 (FoxO3a, also known as FKHRL1) and FOXO4 (AFX) contributes to PI3K/AKT signaling-stimulated cell survival and growth. Activated AKT1 phosphorylates FOXO1 on threonine residue T24 and serine residues S256 and S319 (Rena et al. 1999), FOXO3 on threonine residue T32 and serine residues S253 and S315 (Brunet et al. 1999), and FOXO4 on threonine residue T32 and serine residues S197 and S262 (Kops et al. 1999).

Based on studies with recombinant mouse Foxo6 expressed in the human embryonic kidney cell line HEK293, FOXO6 has two conserved AKT phosphorylation sites: T26 and S184. Mouse Foxo6 has a third predicted Akt phosphorylation site at the C-terminus, T338, which is not present in other Foxo family members and is not conserved in human FOXO6. T26 and S184 are phosphorylated in response to growth factors known to activate PI3K/AKT signaling, but AKT has not been explicitly identified as the responsible kinase. In contrast to other FOXO family members, FOXO6 remains predominantly nuclear irrespective of growth factor-induced signaling, and only a small portion of phosphorylated FOXO6 may shuttle to the cytosol. Phosphorylation of FOXO6 on putative AKT sites, however, may inhibit binding of FOXO6 to target DNA sites (Jacobs et al. 2003, van der Heide et al. 2005).

Protein phosphatase DUSP6 (MKP3) may act to dephosphorylate FOXO1 after AKT-mediated phosphorylation (Rodrigues et al. 2017).

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## Editions

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